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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/088,970
Filing Date: July 19, 2002
Appellant(s): YIP ET AL.

Kenneth A. Weber
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 01/17/2008 appealing from the Office action mailed 6/05/2007.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Diamandis, E.P. (J. National Cancer Institute 2004; 96: 353-356)

Diamandis et al. (Clinical Cancer Research 2005; 11: 963-956)

Grizzle et al. (Cancer Informatics 2005; 1: 86-97)

Adam et al. (Cancer Research 2002; 62: 3609-3614)

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or

with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 8, 12, 20 and 84-94 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of diagnosing prostate cancer versus benign prostate hyperplasia, the method comprising: (i) obtaining from a subject suspected of having either prostate cancer or benign prostate hyperplasia a sample containing a plurality of prostate related protein markers having apparent molecular weights below 10,000 Da, wherein the sample is from seminal plasma; (ii) determining by mass spectroscopy the intensity of the signal for mass/charge ratios of the plurality of protein markers in the sample, the protein having an apparent molecular weight of less than 10,000 Da; (iii) comparing the intensity of the signal for mass/charge ratios of the plurality of protein markers having apparent molecular weight markers of less than 10,000 obtained from step (ii) with the intensity of the signal for mass/charge ratios of the plurality of protein markers having apparent molecular weight markers of less than 10,000 from a control sample where the control sample originates from benign prostate hyperplasia; and (iv) determining whether the comparisons of intensity of the signal for mass/charge ratios obtained in step (iii) is a diagnosis of prostate cancer versus benign prostate hyperplasia, wherein a sample from seminal plasma having a protein characterized by molecular weight of 2776 Da, 4423 Da, 4480 Da, 5753 Da, 6098 Da, 6270 Da, 6998 Da, 7843 Da, 8030 Da, 8240 Da and 8714 Da is a diagnostic of prostate cancer, does not reasonably provide enablement for a method of diagnosing prostate cancer versus benign prostate hyperplasia, the method comprising : (i) obtaining from a subject a sample containing a plurality of prostate related protein markers having apparent molecular weights below 10,000 Da, wherein the sample is selected from the group consisting of prostate tissue, blood, serum, semen, seminal fluid or seminal plasma; (ii) determining by mass spectroscopy a test amount of the plurality of protein markers in the sample, the protein having an apparent molecular weight of less than 10,000 Da; (iii) comparing the test amount of the plurality of protein markers having apparent molecular weight markers of less than 10,000 from a control sample where the control sample originates from benign prostate hyperplasia; and (iv) determining whether the test amount is a diagnostic amount consistent with a diagnosis of prostate cancer versus benign prostate hyperplasia. The specification does not enable any person skilled in the art to which it pertains, or

with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the nature of the invention, (2) the relative skill of those in the art, (3) the breadth of the claims, (4) the amount or direction or guidance presented, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the state of the prior art, and (8) the predictability or unpredictability of the art.

Although the quantity of experimentation alone is not dispositive in a determination of whether the required experimentation is undue, this factor does play a central role. For example, a very limited quantity of experimentation may be undue in a fledgling art that is unpredictable where no guidance or working examples are provided in the specification and prior art, whereas the same amount of experimentation may not be undue when viewed in light of some guidance or a working example or the experimentation required is in a predictable established art. Conversely, a large quantity of experimentation would require a correspondingly greater quantum of guidance, predictability and skill in the art to overcome classification as undue experimentation. In Wands, the determination that undue experimentation was not required to make the claimed invention was based primarily on the nature of the art, and the probability that the required experimentation would result in successfully obtaining the claimed invention. (Wands, 8 USPQ2d 1406) Thus, a combination of factors which, when viewed together, would provide an artisan of ordinary skill in the art with an expectation of successfully obtaining the claimed invention with additional experimentation would preclude the classification of that experimentation as undue. A combination of Wands factors, which provide a very low likelihood of successfully obtaining the claimed

invention with additional experimentation, however, would render the additional experimentation undue.

The nature of the invention

The claims are drawn to a method of diagnosing prostate cancer versus benign prostate hyperplasia, wherein a sample containing a plurality of proteins having apparent molecular weights below 10,000 Da is compared to a control sample containing a plurality of proteins having apparent molecular weights below 10,000 Da where the control sample originates from benign prostate hyperplasia. The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Level of skill in the art

The level of skill in the art is deemed to be high, generally that of a PhD or MD.

The breadth of the claims

Applicants broadly claim a method of diagnosing prostate cancer versus benign prostate hyperplasia, the method comprising : (i) obtaining from a subject a sample containing a plurality of prostate related protein markers having apparent molecular weights below 10,000 Da, wherein the sample is selected from the group consisting of prostate tissue, blood, serum, semen, seminal fluid or seminal plasma; (ii) determining by mass spectroscopy a test amount of the plurality of protein markers in the sample, the protein having an apparent molecular weight of less than 10,000 Da; (iii) comparing the test amount of the plurality of protein markers having apparent molecular weight markers of less than 10,000 from a control sample where the control sample originates from benign prostate hyperplasia; and (iv) determining whether the test amount is a diagnostic amount consistent with a diagnosis of prostate cancer versus benign prostate hyperplasia. As such, the "test amount" is used to determining whether one suffers from prostate cancer or benign prostate hyperplasia.

Guidance in the specification and Working Examples

The specification teaches that the invention provides methods for aiding a prostate cancer diagnosis, which comprises determining a test amount of a marker in a sample from a subject and determining whether the test amount is a diagnostic amount consistent with a diagnosis of prostate cancer (page 2, lines 25-29). With regards to the "test amount", the specification teaches a "test amount of a marker refers to an amount of a marker present in a sample being tested, wherein the test amount can be either in absolute amount or relative amount (page 8, lines 27-29). The specification further teaches (beginning on page 30, Examples) that protein markers were identified using a Ni(II) ProteinChip® Array, H4 ProteinChip® array, and a SCX1 ProteinChip® array, wherein the samples, specifically seminal plasma, were obtained from one BPH (benign prostate hyperplasia) patient and one patient with prostate cancer. With regards to the Ni(II) ProteinChip ® array, the specification teaches (page 30, line 28 to page 32, line 12 and Figure 4) that a number of proteins such as proteins having an apparent molecular weight of about 2776 Da, 4423 Da, 4480 Da, 5753 Da, 6098 Da, 6270 Da, 6998 Da, 8030 Da and 8714 Da, were found to be very abundant in the sample from the prostate cancer patient than in the sample from the BPH patient. Moreover, the specification teaches (page 30, line 28 to page 32, line 12 and Figure 4) that a number of proteins such as proteins having an apparent molecular weight of about 2776 Da, 2905 Da, 3038 Da, 3600 Da, 3835 Da, 3933 Da and 4175 Da, were found to be very abundant in the sample from the BPH patient than a sample from the prostate cancer patient. With regards to the H4 ProteinChip ® array, the specification teaches (page 32, line 15 to page 33, line 23, and Figure 5) that a number of proteins such as proteins having an apparent molecular weight of about 2776 Da, 5753 Da, 6098 Da, 6270 Da, 6998 Da, 7843 Da, 8030 Da and 8240 Da were found to be very abundant in the sample from the prostate cancer patient than the samples from the BPH patient. Furthermore, the specification teaches (page 32, line 15 to page 33, line 23, and Figure 5) that a number of proteins such as proteins having an apparent molecular weight of about 2776 Da, 6098 Da, 6270 Da, 6998 Da, 7843 Da and 8030 Da were also bound and detected using the Ni (II) ProteinChip ® array. With regards to SCX1 ProteinChip® array, the specification teaches (page 33, line 25 to page 34, line 23 and Figure 6) that a protein having an apparent molecular weight of about 5753 Da was present at a high level (relative intensity of about 52) in the sample of the prostate cancer patient. Thus,

while the specification clearly teaches that a sample obtained from seminal plasma having a protein characterized by a molecular weight of 2776 Da, 4423 Da, 4480 Da, 5753 Da, 6098 Da, 6270 Da, 6998 Da, 7843 Da, 8030 Da, 8240 Da and 8714 Da is a diagnostic of prostate cancer versus benign prostate hyperplasia, the specification appears to be silent on any other proteomic profiles obtained from any sample which can be used for a diagnostic amount consistent with the diagnosis of prostate cancer versus benign prostate hyperplasia.

Quantity of experimentation

The quantity of experimentation in the area of proteomics for diagnosis and/or differentiation of prostate cancer vs. benign prostate hyperplasia is extremely large given the infancy of using this technology for diagnostic purposes.

The unpredictability of the art and the state of the prior art

The state of the art at the time of filing was such that one of skill could recognize the unpredictability of using proteomic profiling in a diagnostic setting. For example, Diamandis, E.P. (J. National Cancer Institute 2004; 96: 353-356, *of record*) discusses the potential problems in the analysis of serum proteomic patterns for early cancer diagnosis. These problems for identifying tumor markers include the mechanisms by which tumor markers are released into the circulation, their abundance in biologic fluids, their metabolism and excretion, their dynamic relationship within the host, the clinical samples used, the mass spectrometry instrument and/or the bioinformatic analysis (page 353, 1st column, 3rd paragraph). For instance, Diamandis teaches that discrepancies in the discriminatory peaks (i.e., peaks representing molecules that appear or disappear during cancer progression, or whose amounts differ in cancerous versus noncancerous tissue) identified by four different papers by three different research groups suggests that serum proteomic patterns obtained by the SELDI-TOF technique may not be reproducible within a group or among groups of investigators for the same type of cancer, even when the general analytical methods or datasets are the same (page 353, 1st column, 4th paragraph). Regarding the clinical samples, Diamandis teaches that it is still unknown whether the proteomic patterns will differ between plasma and serum, or how they are affected by the number of freeze thaw cycles or its length of storage (page 354, 1st column, last paragraph). More recently, Diamandis et al. (Clinical Cancer Research 2005; 11: 963-

965, *of record*) teach that while the original papers on serum proteomic profiling for diagnosis of various forms of cancer reported impressive results, these results have not been reproduced by other laboratories and the method has not been validated (page 964, 2nd column, 1st full paragraph). Specifically, Diamandis et al. teach that using peaks of unknown identity for diagnostic purposes should not be a reason a reason to invalidate the method; instead, as Ranshoff points out, it will be important to examine "if this technology does work" and leave the question of "how it works" for investigation at a later time. However, Diamandis points out that precautionary measures about sample collection, processing, and patient selection must be seriously considered to avoid biases (page 964, 2nd column, 1st full paragraph). Along the same lines, Grizzle et al. (Cancer Informatics 2005; 1: 86-97, *of record*) teach that the use of any multiplex mass spectroscopy based approach, as in the analysis of bodily fluids to detect a disease, must be analyzed with great care due to the susceptibility of multiplex and mass spectroscopy methods to biases introduced via experimental design, patient samples, and/or methodology (abstract). In particular, Grizzle et al. teach that specific biases include those related to experimental design, patients, samples, protein chips, chip reader and spectral analysis (abstract). Regarding the biases based on patients, Grizzle et al. teach that these biases include demographics (e.g., age, race, ethnicity, sex), homeostasis (e.g., fasting, medications, stress, time of sampling), and the site of analysis (hospital, clinic other) (beginning on page 88, 2nd column to page 92, 1st column). Regarding the biases in samples, Grizzle et al. teach that the biases in samples include conditions of sampling (type of sample container, time of processing, time to storage), conditions of storage (time and temperature of storage), and prior manipulation (freeze thaw cycles)(beginning on page 92, 1st column to page 93, 1st column), experimental design, patient samples, and/or methodology (abstract). These references demonstrate that there are a number of different biases that need to be considered prior to providing a diagnosis of a diseases based on proteomic profiling.

Conclusion

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the lack of guidance provided in the specification for correlation in vitro results to in vivo success, and the negative teachings in the prior art balanced only against the high

skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as written.

(10) Response to Argument

In response to the rejection, Appellants argue that the invention as claimed does not require very much technical description to enable this invention since the claims only require that you produce an MS profile of the peaks representing proteins of less than 10,000 Da from the variously described samples. With regards to the Examiner's concerns, Appellants submit that the Examiner's concerns are the failure of Appellants to provide results for samples other than seminal plasma, and failure of the Appellants to recite the nine specific markers in the claims. With regards to the first concern, Appellants submit that post-fling publications have been submitted along with a rule 132 Declaration by Dr. Tai-Tung Yip describing the use of both blood and prostate samples to distinguish between BPH and prostate cancer (see Evidence Appendix-page 15). However, Appellants assert that the Examiner is silent as to why this evidence does not fully address his concern. Secondly, Appellants argue that the recitation of specific markers in the claims will deny the Appellants the benefit of their true contribution, which is not the discovery of specific markers for detecting prostate cancer, but rather, the discovery that MS can be used to cost effectively distinguish between BPH and prostate cancer by detecting elevated levels of generalized protein degradation. Moreover, Appellants submit that the Examiner's Wands' concerns are fully addressed by Dr. Yip's Rule 132 Declaration and attached evidence, or are based upon irrelevant facts that even if accurately stated do not have an impact on the legal question of whether the claims are enabled. For example, Applicants assert the following:

The Nature of the Invention:

Appellants argue that according to the Examiner, the invention is classified within the unpredictable art of chemistry and biology; and says nothing more. However, Appellants point out that the Federal Circuit in Mycogen did not make a statement that biology and chemistry are unpredictable arts with regards to enablement, but instead explained that simultaneous conception and reduction to practice occurs in unpredictable arts such as chemistry and biology. In addition, Appellants assert that in the context of the present invention, it is true that the relevant scientific findings were not predictable from the prior art, and thus, the invention is non-obvious. However,

Appellants assert that once discovered, the use of MS to distinguish between prostate cancer and BPH becomes routine, predictable and reproducible.

Level of Skill in the Art:

Appellants agree with the Examiner that the level of skill in the art is high, but notes that mass spectroscopy is a routine procedure commonly conducted by trained technicians.

The breadth of the claims:

Appellants assert that the Examiner merely restates the pending independent claim, but adds nothing to the calculus of whether the claim scope is overly broad.

Guidance in the Specification:

Appellants assert that the Examiner goes into the details of the depth of the teachings provided by the specification. However, Appellants argue that the sole concern raised was that only one sample source was tested, eg., seminal plasma, which was addressed by Appellants in a submission of declaration and post filing publications describing similar results using blood and prostate tissue. Yet, Appellants argue that the Examiner is silent as to why this submission of evidence did not dispel his concerns that it would require undue experimentation to practice the invention using the different sample sources recited in the claims. As stated in MPEP 2164.04, Appellants argue that the initial burden is on the Examiner to explain why he believes that the other sample sources are not likely to work.

Quantity of Experimentation:

Appellants argue that the Examiner makes an unsupported statement that the area of proteonomics is extremely large, which is an irrelevant truth. In contrast, Appellants assert that while the area of proteomics is an exciting field of unknown potential with much need for experimentation, this truth is irrelevant to the issue before the Board. In the instant case, Appellants assert that the relevant question is whether it requires undue experimentation to practice an invention requiring the steps of: (1) obtaining samples; and (ii) quantifying the proteins in those samples having molecular weights below 10,00 Da using MS.

The unpredictability of the art and the state of the prior art:

In this section, Appellants submit that the Examiner sets forth a number of irrelevant truths and then argues that the pending claims are not enabled. More specifically, Appellants submit that the Examiner relies on Diamandis (2004), Diamandis (2005) and Grizzel (2005), wherein Diamandis

(2004/2005) describes potential problems in the analysis of serum proteomic patterns for detection of cancer. The problems include: how the markers are released into the host serum; their relative abundance; and the dynamic relationship between host, the samples, the MS apparatus, and the bioinformativs used to provide the analysis. In addition, Appellants submit that Diamandis states that markers may vary over time and progression of disease, that different research groups may provide different results; that sample storage and handling will effect the MS profiles of markers. With regards to Grizzle, Appellants assert that Grizzle is cited for mentioning the same concerns and mentioning ethnicity, experimental design, and spectral analysis as additional parameters that need to be evaluated. However, Appellants assert that these multiple concerns involve parameters that are commonly and routinely optimized for any diagnostic assay; and further, Appellants have demonstrated that distinguishing between BPH and prostate cancer using MS profiles can be done using 3 different probes and 3 different sample sources. Moreover, Appellants argue that while the concerns raised by Diamandis and Grizzel are important concerns, they are not relevant inquires for purposes of enablement under 112. Rather, Appellants argue that they are relevant for creating a commercially acceptable kit having the specificity (positive predictive value) and sensitivity (negative predictive value) needed to pass muster with the FDA, not the USPTO.

Appellants further submit that the Examiner in the conclusionary statement raises two additional points that bear comment by Appellants. The first is that the Examiner demands that the claims include a recitation of nine peptide masses, which is the heart of the issue on appeal. In particular, Appellants contend that while the Examiner correctly sets forth the situation that Appellants in the specification and in the Dr. Yip Declaration (attached) have stated that the MS profiles are made up of 9 masses that are reliably and reproducibly detected, what doesn't change is the shifting of the masses below 10,000 Da to lower molecular weights because of increased protease activity in prostate cancer patients compared to those suffering from BPH which is Appellant's invention. Moreover, Appellants submit that the fact that changes in the specific parameters relating to sample preparation and MS analysis might result in different absolute masses does not dictate that the claims require undue experimentation. The second is that the Examiner notes for the first time that the claims are directed to distinguishing between BPH and prostate cancer in healthy people. However, Appellants assert that the claims recite distinguishing between BPH and prostate cancer in subjects and urges that common sense be applied here.

These arguments have been carefully considered, but are not found persuasive.

In response to Appellants arguments, the Examiner acknowledges and does not dispute Appellants assertions that the claims require the active step of producing a MS profile of peaks representing proteins of less than 10,000 Da.. However, the Examiner recognizes that in addition to producing a MS profile of peaks representing proteins of less than 10,000 Da, the claims further require a nexus between the diagnosis of prostate cancer and an increase in the quantity of lower molecular weight proteins of less than 10,000 Da. Thus, this correlation is the issue which the Examiner feels is at the heart of this appeal. In other words, could one of skill in the art predictably diagnose prostate cancer versus benign prostate hyperplasia using mass spectroscopy based on determination of a quantity of lower molecular weight proteins of less than 10,000 Da. without undue experimentation. The Examiner's conclusion in view of the Wands factors as set forth above and further the specification, Yip Declaration and evidence submitted therein is simply that it would require undue experimentation for one of skill in the art to perform the method of the claim as written. For example, the Examiner recognizes that, as stated on page 3 of the Yip declaration filed on 6/26/2006, "The successful use of the prostate classification system described herein relies on the protein fingerprinting of the nine masses. Because these masses were found to be reproducibly reliably detected…." (*Emphasis added*) In other words, while the "inventive principle" uses mass spectroscopy to profile samples, success, e.g., reproducibility, is dependent on the use of the nine protein masses, and not merely the quantity of a plurality of protein markers in a sample. Moreover, while Appellants contend that the Examiner is silent on why the post filing publications and Yip declaration does not fully address the Examiner's concerns regarding Appellants failure to provide results for samples other than seminal plasma, the Examiner recognizes that these publications, as well as the Yip declaration, were addressed in the Office Actions of 9/1/2006 and 6/05/2007. In particular, the Examiner directs Appellants attention to page 9 to page 10 of the 6/05/2007 office Action which states that "…the Examiner recognizes that, as stated on page 3 of the Yip declaration filed on 6/26/2006, "The successful use of the prostate classification system described herein relies on the protein fingerprinting of the nine masses. Because these masses were found to be reproducibly reliably detected…. Moreover, while the specification has taught a number of mass values obtained from a prostate cancer patient's seminal plasma, these mass values do not appear to be identical or reproducible from the mass values obtained from Adam's serum samples or

Cazares et al.'s prostate tissues samples. As such, one of skill would need to first identify mass values from prostate tissue, blood, serum, semen, seminal fluid or seminal plasma, which are reproducibly reliably, detected from each of these samples and than use these mass values for classification and diagnosis. " (*Emphasis added*) Furthermore, careful reconsideration of the post filing publications does not appear to lend support for the scope of the invention as claimed, but instead appears to strengthen the Examiners position that specific mass values are required.. For example, the Adam's publication teaches that "The successful use of the prostate classification system described herein relies entirely on the protein fingerprint pattern of the nine massess. Because these masses were found to be reproducibly reliably detected...." (page 3614, 1st column, 1st full paragraph). In addition, Cazares et al. concludes with "… differential SELDI protein profiles were observed for cell lysates prepared from microdissected normal BPH, PIN, PCA and epithelial cells. Several small molecular mass species were found to be overexpressed in PIN, and because they were also overexpressed in PCA, these proteins may represent early signals or signatures of developing cancer. Additionally, one marker at 5666 Da was found to be increased in BPH and may have the ability to distinguish BPH from PCA." (page 2550, 2nd column, last paragraph). Next the Examiner would like to address Appellants arguments pertaining to Examiners Wands factors with the following points:

- Nature of the Invention:

The Examiner acknowledges and does not dispute Appellants assertions that the Federal Court in Mycogen did not specifically make a statement that biology and chemistry are unpredictable arts with regards to enablement. However, the Examiner recognizes that the Federal Court clearly associates chemistry and biology as being an unpredictable art, in general regardless of what statute is in question. In addition, the Examiner acknowledges and does not dispute Appellants assertions that once discovered, the use of MS to distinguish between prostate cancer and BPH becomes routine, predictable and reproducible. However, as stated in the Yip declaration as noted above, this can only occur when one identifies specific masses which are reproducibly and reliably detected.

- Level of Skill in the Art:

The Examiner agrees with Appellants assertions regarding the Level of Skill in the Art.

- The breadth of the claims:

Regarding Appellants assertions regarding the breadth of the claims, the Examiner acknowledges and does not dispute Appellants assertion that the Examiner adds nothing to the calculus of whether the claim scope is overly broad. However, the Examiner recognizes the claims recitation of a plurality of proteins having apparent molecular weights below 10,000 Da speak for themselves given the sensitivity of mass spec to detect small quantities of proteins and fragments thereof.

- Guidance in the Specification:

Regarding Appellants arguments pertaining to the guidance in the specification, the Examiner believes that these concerns regarding the evidence, e.g., declaration and post-filing publications, have been addressed by the Examiner above and are incorporated herein.

- Quantity of Experimentation:

Regarding Appellants argument that the Examiner makes an unsupported statement that the area of proteomics is extremely large, the Examiner recognizes that this statement in relation to using proteomics in the context of diagnosis is support by the state the art, as well as Appellants submission that "the area of proteomics is an exciting field of unknown potential with much need for experimentation" (*emphasis added*).

- The unpredictability of the art and the state of the prior art:

Regarding Appellants arguments pertaining to the unpredictability of the art and the state of the prior art, the Examiner acknowledges and has stated on record (Office action of 9/01/2006, page 14) that " the Examiner agrees with the following: 1) the abundance of lower weight proteins in prostate cancer samples can be detected with other MS probe surfaces; 2) the abundance of lower weight proteins in prostate cancer samples can be detected in other patients; 3) the abundance of lower weight proteins in prostate cancer patients can be detected in samples other than serum; and 4) that the secondary issues can be routinely addressed by competent laboratory technicians." Thus, the Examiner agrees that the many of the concerns raised by Diamandis and Grizzel can be commonly and routinely optimized for any diagnostic assay as asserted by Appellants. However, the Examiner recognizes, as noted in the Yip Declaration as a quotation from Adam (page 3 of Yip), "The successful use of the prostate classification system described herein relies on the protein fingerprinting of the nine masses. Because these masses were found to be reproducibly reliably detected, only the mass values are required to make correct classification or diagnosis." In other

words, it appears that one of skill must first identify a reproducible mass value and than use this mass value for correct classification and diagnosis. In the instant case, the claims encompass determining by mass spectroscopy a test amount of a plurality of protein markers in a sample, the protein markers having an apparent molecular weight of less than 10,000 Da and comparing a test amount of the plurality of protein markers having an apparent molecular weight of less than 10,000 Da with an amount of a plurality of protein markers having an apparent molecular weight of less than 10,000 Da from a control sample where the control sample originates from benign prostate hyperplasia and determining if the test amount is a diagnostic amount consistent with a diagnosis of prostate cancer versus benign prostate hyperplasia. While, the specification has taught a number of mass values obtained from a prostate cancer patient's seminal plasma, these mass values do not appear to be identical or reproducible from the mass values obtained from Adam's serum samples or Cazares et al.'s prostate tissues samples. As such, one of skill would need to first identify mass values from prostate tissue, blood, serum, semen, seminal fluid or seminal plasma, which are reproducibly reliably, detected from each of these samples and than use these mass values for classification and diagnosis.

With regards to Appellants arguments pertaining to the two additional points, the Examiner recognizes that the first point was raised in the Non-Final Office Action of 9/01/2006 and has been fully addressed above and incorporated herein. With regards to Appellants arguments pertaining to the second point, the Examiner acknowledges and does not dispute Appellants assertions that the claims specifically recite distinguishing between BPH and prostate cancer in *subjects*. As such, the Examiner, after careful reconsideration, agrees with Appellants assertions that this does not encompass normal healthy individuals.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Brandon J. Fetterolf, PhD

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